

Comment

metabolic syndrome, and diabetes.³ Combining nebivolol and valsartan within a fixed combination is therefore an attractive therapeutic option in view of its antihypertensive efficacy, good tolerability, and potential value for prevention of cardiovascular and renal complications in patients with hypertension. However, this potential remains to be tested in clinical trials with hard clinical endpoints.

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- Giles TD, Weber MA, Basile J, et al, for the NAC-MD-01 Study Investigators. Efficacy and safety of nebivolol and valsartan as fixed-dose combination in hypertension: a randomised, multicentre study. *Lancet* 2014; **383**: 1889–98.
- James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; **311**: 507–20.
- Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; **31**: 1281–357.
- National Institute for Health and Care Excellence. Hypertension: clinical management of primary hypertension in adults. 2011. <http://guidance.nice.org.uk/CG127/NICEGuidance/pdf/English> (accessed May 19, 2014).
- Chrysant SG, Chrysant GS. Current status of beta-blockers for the treatment of hypertension: an update. *Drugs Today (Barc)* 2012; **48**: 353–66.
- Gorre F, Vandekerckhove H. Beta-blockers: focus on mechanism of action. Which beta-blocker, when and why? *Acta Cardiologica* 2010; **65**: 565–70.
- Markham A, Goa KL. Valsartan. A review of its pharmacology and therapeutic use in essential hypertension. *Drugs* 1997; **54**: 299–311.
- Traynor K. New β -blocker gets FDA approval. *Am J Health Syst Pharm* 2008; **65**: 190.
- Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003; **326**: 1427–31.
- Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; **359**: 2417–28.
- Fenichel RR, Lipicky RJ. Combination products as first-line pharmacotherapy. *Arch Intern Med* 1994; **154**: 1429–30.
- O'Brien E, Parati G, Stergiou G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens* 2013; **31**: 1731–68.



Focus on blood pressure as a major risk factor

See [Editorial](#) page 1861

See [Articles](#) page 1899

The main risk factor for disease and premature death worldwide is high blood pressure.¹ The associations between blood pressure and fatal coronary artery disease and fatal stroke have been well demonstrated.² However, little evidence exists from contemporary clinical practice on the associations between blood pressure and morbidity and mortality from specific cardiovascular disease conditions in different age groups. Also missing are results concerning lifetime risk for specific cardiovascular complications associated with hypertension. Eleni Rapsomaniki and colleagues³ now report results in *The Lancet* that extend our knowledge and understanding of blood pressure as a risk factor for cardiovascular disease. This contemporary study in a primary-care setting assessed electronic health records for more than a million patients aged 30 years or older who did not have cardiovascular disease, and recorded initial cardiovascular morbidity during a median of 5.2 years of follow-up.

The investigators report that the lifetime burden of hypertension is substantial. In a 30-year-old patient with hypertension, the lifetime risk for a cardiovascular

event was 63.3% (95% CI 62.9–63.8), compared with 46.1% (45.5–46.8) in a normotensive individual, with an estimated loss of 5 years free of cardiovascular disease. Whereas patients with moderate or severe hypertension should always be offered antihypertensive treatment, the benefit of treatment in patients with mild hypertension has been subject to discussion.⁴ However, the results by Rapsomaniki and colleagues³ provide circumstantial support for starting treatment of mild hypertension in younger people.

In each age group, the risk for future cardiovascular disease was lowest in people with a systolic blood pressure of 90–114 mm Hg and a diastolic blood pressure of 60–74 mm Hg, and no increase in risk with low values (J-shaped curve) was noted. A novel finding was that the risk associated with an increase in blood pressure differed with age and specific cardiovascular disease conditions. For example, the associations between morbidity and an increase in systolic blood pressure were strongest for stable angina pectoris (hazard ratio for a 20 mm Hg rise in systolic blood pressure 1.41, 95% CI 1.36–1.46), and intracerebral and subarachnoidal haemorrhage (1.44 [1.32–1.58] and

1.43 [1.25–1.63], respectively), whereas the risk of an abdominal aortic aneurysm was more closely related to increased diastolic blood pressure (hazard ratio for a 10 mm Hg rise in diastolic blood pressure 1.45, 1.34–1.56). Furthermore, for patients aged 30 years, coronary artery disease accounted for most of the estimated loss of years free of cardiovascular disease associated with hypertension, whereas heart failure contributed to a substantial part in patients aged 80 years. Most patients with heart failure are old, have an impaired quality of life and poor prognosis, and health-care costs are high.⁵ The findings by Rapsomaniki and colleagues³ indirectly support antihypertensive treatment also in patients 80 years or older.⁶

Although the efficacy of antihypertensive drug therapy is undisputed, observational studies suggest that few patients reach target blood pressure.⁷ Several steps therefore need to be taken to improve antihypertensive treatment and control (panel). First, assessment of global cardiovascular risk is essential to offer the best management to the individual patient. The study by Rapsomaniki and colleagues³ provides important new information to improve risk assessment, patient counselling, and decision making for patients with hypertension. Second, improvements are needed in caregiver support and education. Caregivers might think that side-effects with treatment are a problem, or that available evidence to treat is insufficient. Drugs might be prescribed with an inappropriate dosing, or inadequate drug combinations could be used. Caregiver organisation and systematic follow-up might also need improvement.

Third, factors that can improve drug compliance and treatment persistence to prescribed therapy ought to be better understood than they are at present. We reported that 35% of patients newly initiated on antihypertensive drug therapy discontinued treatment within 2 years.⁸ Furthermore, many patients referred for apparently treatment-resistant hypertension do not seem to take their prescribed medication.^{9,10} Fourth, an increased use of home blood-pressure monitoring and 24 h ambulatory blood-pressure monitoring is important. Such use would identify patients susceptible to the white-coat effect, improve risk stratification, and increase patient engagement.¹¹ Fifth, people with secondary forms of hypertension can often be offered specific treatment and are thus important to identify,

Panel: Key issues to improve antihypertensive treatment and control

- Assessment of global cardiovascular risk in individual patients
- Improve caregiver organisation, support, and education
- Increase drug compliance and treatment persistence to prescribed treatment
- Expand the use of home blood-pressure monitoring and 24 h ambulatory blood-pressure monitoring
- Consider secondary forms of hypertension in difficult-to-treat patients
- Consider referral of patients with remaining uncontrolled hypertension to a specialist hypertension centre

in particular those with apparently treatment-resistant disease. Finally, an appreciation is needed that most patients with remaining uncontrolled hypertension can be well controlled when referred to a specialist hypertension centre.^{10,12}

Blood-pressure control could be improved in patients with hypertension. The clinical benefit of improved risk assessment and appropriate treatment might be substantial.

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- 1 Lim SS, Vos T, Flaxman AD, Danaei G, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2224–60.
- 2 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903–13.
- 3 Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet* 2014; **383**: 1899–911.
- 4 Diao D, Wright JM, Cundiff DK, Gueyffier F. Pharmacotherapy for mild hypertension. *Cochrane Database Syst Rev* 2012; **8**: CD006742.
- 5 Mejhert M, Lindgren P, Schill O, et al. Health care consumption and cost expenditure in chronic systolic heart failure during an 8–12 year prospective follow up. *Eur J Intern Med* 2013; **24**: 260–65.
- 6 Beckett NS, Peters R, Fletcher AE, et al, for the HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; **358**: 1887–98.
- 7 Qvarnström M, Wettermark B, Ljungman C, et al. Antihypertensive treatment and control in a large primary care population of 21167 patients. *J Hum Hypertens* 2011; **25**: 484–91.
- 8 Qvarnström M, Kahan T, Kieler H, et al. Factors associated with persistence to antihypertensive treatment. *Eur J Clin Pharmacol* 2013; **69**: 1955–64.

- 9 Strauch B, Petrák O, Zelinka T, et al. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. *J Hypertens* 2013; **12**: 2455–61.
- 10 Fadl Elmula FE, Hoffmann P, Fossum E, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension after witnessed intake of medication before qualifying ambulatory blood pressure. *Hypertension* 2013; **62**: 526–32.
- 11 Redon J, Campos C, Narciso ML, et al. Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. *Hypertension* 1998; **31**: 712–18.
- 12 Persu A, Jin Y, Baelen M, et al; European Network Coordinating research on REnal Denervation (ENCOREd) Consortium. Eligibility for renal denervation: experience at 11 European expert centers. *Hypertension* 2014; **63**: 1319–25.

The drugs do work: blood pressure improvement in England

See [Editorial](#) page 1861

See [Articles](#) page 1912

Raised blood pressure is the leading risk factor for global disease burden; consequently, recognition and treatment is a key activity in primary care. Similarly, many public health initiatives aim to reduce the population burden through reduction of salt consumption, alcohol consumption, and obesity with policies intended to increase exercise and healthy diets.¹

In *The Lancet*, Emanuela Falaschetti and colleagues² report unique data from the Health Survey for England based on a sample of 4540 people for 2011, showing how detection and control of raised blood pressure has changed in successive samples over a 17-year period from 1994. Mean systolic blood pressure has fallen by about 5 mm Hg systolic in men and 9 mm Hg in women, although the prevalence of hypertension has remained constant. Greater than 50% more people were receiving treatment for hypertension in 2011 than in 1994, and the proportion of those on treatment whose blood pressure was controlled to 140/90 mm Hg nearly doubled; as a result, people on treatment in 2011 had a 13 mm Hg (in men) to 16 mm Hg (in women) lower blood pressure than did people in 1994, which is

associated with more intensive therapy. These secular changes were not adjusted for changes in age in the population, but the age structure of the population in England has remained fairly stable over this period.³

The cross-sectional nature of Falaschetti and colleagues' data make secular changes difficult to interpret; the reduction in mean blood pressure in people with treated hypertension might partly result from lower thresholds for initiation of blood pressure treatment, for example in people with existing cardiovascular disease or diabetes, who make up between 15% and 20% of the study population.^{1,2} Similarly, it is difficult to infer what the fall in blood pressure in untreated people was in this study period, because people with high blood pressures in 2011 were more likely to be treated than in 1994. Nevertheless, overall the data convey a positive message, and the reported reductions in blood pressure will have made a major contribution to the fall in cardiovascular mortality reported in this period.^{4,5} The study benefits from consistent and carefully protocolised methods over time, although the monitor used to measure blood pressure did change in 2003, which has been taken into account.² It is likely that the estimates of hypertension prevalence are exaggerated because of measurement of blood pressure on one occasion as opposed to the multiple and out-of-office methods recommended in national and international guidelines.^{1,6} However, nurse measurement of blood pressure, as in Falaschetti and colleagues' study, is systematically lower than that measured by a doctor, which will tend to mitigate against this factor.⁷

In terms of non-pharmacological effects, the authors mention the potential effects of salt reduction in the national diet, and other measures from the same survey allow consideration of lifestyle; changes in weight (5 kg increase) and alcohol consumption (a third of the population now drink more than 3–4 units on the heaviest drinking day in the past week) would be expected to increase blood pressure, but improved physical activity

